EFFICACY, EFFECTIVENESS, AND SAFETY OF COMBINATION CREAM (CLINDAMYCIN 3%, TRETINOIN 0.05%, AND DEXAMETHASONE 0.05%) OVER THEIR MONOTHERAPY (TRETINOIN 0.05%) IN ACNE VULGARIS PATIENTS: SCALED-UP RETROSPECTIVE COHORT STUDY

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ABSTRACT

Acne vulgaris is an inflammatory disorder that impacts pilosebaceous glands, affecting many adolescents physically and psychologically. The finest acne cream comprises retinoids, antibiotics, and corticosteroids. Accuracy of acne vulgaris therapy affects the healing and prognosis. To compare the efficacy of a single topical cream containing 0.05% Tretinoin to a combination cream containing Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%. This was a retrospective cohort study that included 1027 respondents, observing the result of using 2 types of creams for treating acne: 1) a single tretinoin 0.05% cream and 2) a combination cream therapy (Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%). The evaluated parameters were mean reduction in acne lesions quantity as the main objective and other side parameters (Spot, Pore, Wrinkle, UV moisture, UV damage, Roughness, Porphyrin, Pigmentation, and Hydration) as the secondary goals. This study shows that there was a significant difference both in primary and secondary endpoints between single tretinoin 0.05% cream and combination cream therapy (Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%) with p-value <0.05 in all parameters. As for adverse events, there was no statistically significant difference locally, and no incidence was found systemically. Combination cream (Clindamycin 3%, Dexamethasone 0.05%, and Tretinoin 0.05%) might provide superior primary and secondary efficacy parameters in acne treatment than single tretinoin cream.

Keywords: Acne vulgaris, Safety, Effectiveness, Tretinoin, Clindamycin, Dexamethasone

INTRODUCTION

The familiar yet chronic skin disorder, acne vulgaris, is recognized by the inflammation or localized inflammation of the sebaceous glands (Lynde et al., 2019; Rao et al., 2021). This skin disorder can manifest in various forms, with pleomorphic arrangement in most cases. The arrangement could be made of comedones, papules, pustules, or nodules. The manifestation in females comes earlier than in males, affected by puberty and hormones (Azarchi et al., 2019). All women of all races can be affected by acne, from Africa and America (37%), Hispanic (32%), Asian (30%), Caucasian (24%), and Indian (23%) (Perkins et al., 2011). High

prevalence (47-90%) is mainly found in adolescents. The prevalence of acne vulgaris is increasing yearly, as demonstrated by the statistics from Indonesian Cosmetics Dermatology Research, where the number of people with acne vulgaris rose from 60% in 2006, 80% in 2007, and 90% in 2009 (Purwaningdyah, 2013). Prevalence of 83-85% is found in female teenagers (age 14-17), and 95-100% found in male adolescents (age 16-19) (Thiboutot & Zaenglein, 2014). Four factors can cause acne: (1) follicular clogging caused by follicular epidermal hyperproliferation; (2) excessive production of sebum; (3) inflammation; and (4) the activity of *Propionibacterium acnes* (*P. acnes*) (Cong et al., 2019). It is a complex condition involving many factors, from psychological stress, infection, work, food/diet, climate, environment, skin type, hygiene, cosmetic use, genetics, ethnicity, and race (Ghodsi et al., 2009). The predilection areas for acne are the face, shoulders, upper superior extremities, chest, and back. It is not a lethal disease but for those affected, teens in particular, it has a significant impact both physically and psychologically, causing worry, despair, and low self-confidence (Eyüboglu et al., 2018).

The critical factors for a patient's recovery and prognosis are accuracy and speed in treating acne vulgaris (Afriyanti, 2015). The best acne treatments are antibiotics to suppress the growth of bacteria, corticosteroids to reduce inflammation, and retinoids to reduce the formation of microcomedones. Since all the components can be incorporated into a single cream, combining anti-acne creams is one of the best ways to treat acne. Being reasonably inexpensive, non-invasive, practical, and has fewer adverse effects than other treatments made the researchers favor the combination of anti-acne creams (Zeichner, 2012).

The research question in this study is "Is there any difference in the result of acne treatment using single versus combination topical cream?". This is a large-scale retrospective cohort study aiming to compare the efficacy along with clinical improvements, side effects, and patient satisfaction of a single topical cream containing 0.05% Tretinoin to a combination cream containing Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%.

LITERATURE REVIEW

Acne vulgaris is a disorder of the skin involving pilosebaceous unit, involving Propionibacterium acnes proliferation and other inflammation components, especially in the perifollicular area, such as leukocytes; chemokines; and proinflammatory cytokines from keratinocytes and sebocytes, debris blockage of follicular opening, excess sebum production, hyperkeratinization of the follicle, and many others (Titus & Hodge, 2012; Toyoda & Morohashi, 2001). As it affects a lot of people, especially adolescents, physically and psychologically, giving proper and prompt treatment will result in better results and prognosis, thus improving the quality of life of its bearer (Kraft & Freiman, 2011). Treatment of acne aims to improve skin lesions and reduce their severity and recurrences. It also includes reducing obesity and diet modification, which suggests acne patients to consume low glycemic index diet, with higher soluble fiber content and less fat, minding sugar and starch type, food form, also how the foods are processed/ cooked. (Kraft & Freiman, 2011; Oon et al., 2019; Titus & Hodge, 2012).

Combination topical treatment is much preferred than a single

active component to be used alone (either for antibiotics benzoyl peroxide, or retinoids). A lot of previous studies and guidelines strongly recommend combination of antimicrobials (antibiotics or benzoyl peroxide) with retinoids for treatment choice. Systemic antibiotics should be limited to reduce the chance of developing resistance and other antibiotics-related complications and use in concordance with topical medication (Kraft & Freiman, 2011; Oon et al., 2019; Reynolds et al., 2024).

METHOD AND MATERIAL

Study Population

All patients aged 12 years or above with acne vulgaris as the clinical diagnosis were included as the sample population for this study. The severity of acne vulgaris is based on the number of lesions: mild cases having fewer than 20 comedones; 15 inflammatory lesions; or fewer than 30 total lesions, moderate cases having between 20 and 100 comedones; 15 to 50 inflammatory lesions; or fewer than 30 to 125 total lesions, and severe cases having more than 5 cysts; more than 100 comedones; more than 50 inflammatory lesions; or more than 125 total lesions.

Age requirements of at least 12 years old, acne vulgaris in the face region, independent of skin tone, consenting to therapy with informed consent, Investigator's Static Global Assessment (ISGA) score of 3 (moderate) or 4 (severe), and complete medical records were also required. Patients with any skin disease on the face, including rosacea, impetigo, viral and fungal infections, atopic or contact dermatitis, acneform eruptions, or any usage of oral tretinoin and steroids within 4 weeks, and any respondents who were suspected allergic to the active ingredients in the anti-acne cream combination, were excluded in this study.

The study was carried out following the Declaration of Helsinki's ethical principles, the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice, and applicable regulatory requirements. This study was granted ethical clearance by the Universitas Tarumanagara Human Research Ethics Committee Institute of Research and Community Engagement (Registration Number: PPZ20192057 and Letter Number: 1681-Int-DIR-KLPPM/Untar/X/2019).

Study design

Retrospective cohort research was done for this study at the Sukma Clinic with the sample selection done based on the previously mentioned inclusion and exclusion criteria. Using patients' data that were registered from January 2019 to December 2022, this study was conducted in December (having completed 4 weeks of treatment). Non-Random Consecutive Sampling is the sampling technique utilized in this investigation.

Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05% were the active ingredients in the anti-acne cream formulation, while the comparator medication was 0.05% tretinoin in a normal regimen. For four weeks, all patients from every group were told to apply a fingertip of the assigned study drug to the acne lesions on the face. Patients were instructed to clean their faces with warm water and light soap, and then pat the skin dry before applying the medication. It was advised to wash hands properly before and after applying the medication. The drug should not be used on the mucous membranes around the eyes, mouth, nose, or angles. To reduce the risk of sunburn

and photosensitivity, patients were advised to wear sunscreen and to stay away from UV light, sunlamps, and other medications that could make them more sensitive to sunshine. Topical emollient lotions were permitted to keep the skin moist during the trial period.

Study endpoint

The mean percent change and overall mean reduction in acne lesions quantity from baseline to the fourth week served as the primary effectiveness objective (inflammatory, noninflammatory, and total lesion count). The secondary objectives were mean current change and overall mean reduction in the side parameter from baseline to week 4 (Spot, Pore, Wrinkle, UV moisture, UV damage, Roughness, Porphyrin, Pigmentation, and Hydration). To compare side parameters, digital observation was used, with assistance from artificial intelligence (Software from Langdi).

The percentage of patients with an ISGA score improvement of two grades from baseline to week 4 and who were evaluated as "clear" or "near clear" were the tertiary goals. In week 4 (or the early discontinuation visit), the investigator assessed the physician's global evaluation of efficacy score and classified it as "Excellent," "Good," "No change," "Bad," and "Worse." The Cardiff Acne Disability Index (CADI) was also examined from baseline to week four in this study.

Adverse effects (AEs) and laboratory tests were monitored to gauge safety. The patient and the doctor conducted local tolerability assessments, which were recorded in the patient's diary. A doctor assessed the local tolerability at each visit based on the degree of scaling and erythema (none (grade 0) to severe (grade 3)). During the research period, every day patients were requested to take notes about their skin if there was any itching, burning, or stinging (none to severe (rate 0 to 3)).

Statistical analysis

According to prior studies, the minimal sample size for each group was 250 respondents, with an 80% power level, 5% superiority margin, and 5% significance level to identify a statistically significant difference between the two groups. Analysis of descriptive data was based on the data's nature. Quantitative data will be displayed with a mean, standard deviation, median, minimum, and maximum, whereas qualitative data will be presented with proportions (%).

Data analysis regarding the relationship between variables is adjusted to the type of data for each variable. If the two variables are qualitative data, the statistical test used is Pearson Chi-Square with Fisher Exact as an alternative test. For the paired type of categorical-numeric data, the Paired T-test statistic test will be used, and the Wilcoxon as an alternative. For non-paired categorical-numeric data types, the Independent T-test is used as a statistical test or the Mann-Whitney test as an alternative. To determine the data distribution Kolmogorov Smirnov test will be used (p-value> 0.05). A p-value with a significance limit of 0.05 expresses the relationship between variables.

RESULTS

This study included 1027 respondents who met the inclusion criteria. All demographic data of respondents starting from gender, age, duration of acne disease, number of lesions before therapy, degree of acne, ISGA Score, and CADI score are presented in Table 1. In this research, most respondents were men (61,1%) with a mean age

of 23 years old, had acne for 1-6 months, had moderate acne severity (54,7%), and had severe ISGA and CADI scores.

Table 1. Basic and Clinical Characteristics of Research Respondents

Variable	Combination Cream (N=774)	Tretinoin 0.05% (N = 253)
Sex, n (%)		
• Men	473 (61,1%)	124 (49,0%)
• Women	301 (38,9%)	129 (51,0%)
Age (years), median (range)	23 (12 – 43)	21 (12 – 42)
Duration of acne (months), n (%)		
• <1	4 (0,5%)	2 (0,8%)
• 1-6	412 (53.2%)	132 (52,2%)
• 7-12	253 (32,7%)	75 (29,6%)
• 13-24	70 (9,0%)	31 (12,3%)
• 25-48	35 (4,5)	15 (5,9%)
Baseline acne lesion count, median (range)		
• Facial inflammatory lesion (Total)	29 (0 – 60)	25 (0 – 60)
• Facial non-inflammatory lesion (Total)	60 (0 – 135)	63 (1 – 135)
• Facial cysts lesion (Total)	3 (0 – 6)	3 (0 – 6)
• Total lesion count	92 (9 – 193)	95 (10 – 194)
Degree of Acne Severity (baseline), n (%)		
• Mild	136 (17,6%)	17 (6,7%)
• Moderate	423 (54,7%)	166 (65,6%)
• Severe	215 (27,7%)	70 (27,7%)
Secondary Parameter Baseline (by AI Measurement), median (range):		
• Spot	17 (13 – 55)	16 (13 – 55)
• Pore	28 (13 – 63)	31 (13 – 56)
• Wrinkle	31 (12 – 65)	32 (12 – 59)
• UV Moisture	52 (16 – 87)	54 (25 – 78)
• UV damage	34 (17 – 69)	34 (17 – 64)
• Roughness	31 (16 – 59)	30 (16 – 53)
• Porphyrin	59 (14 – 85)	59 (20 – 82)
• Pigmentation	45 (18 – 94)	47 (32 – 82)
• Hydration	51 (40 – 60)	50 (36 – 60)
Baseline ISGA score, n (%)		
• Clear (Grade 0)	0	0
• Almost clear (Grade 1)	0	0
• Mild (Grade 2)	0	0
• Moderate (Grade 3)	332 (42,9%)	124 (49%)
• Severe (Grade 4)	442 (53,1%)	129 (51%)
CADI Score, n (%)		
• Clear (0)	0	0
• Mild (1-4)	0	0
• Moderate (5-9)	297 (38,4%)	110 (43,5%)

• Severe (10-15)	477 (61,2%)	143 (56,5%)

*Combination Cream: Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%.
ISGA: Investigators Static Global Assessment
CADI: Cardiff Acne Disability Index

Efficacy analysis of the primary and secondary parameters of the 2 types of anti-acne therapy is presented in Table 2. There is a significant difference between single cream and combination cream in all the parameters of primary, secondary, and tertiary endpoints (p-value <0.05). Combination Cream also demonstrated greater efficacy with reductions of 90 (13-100) for facial inflammatory lesions, 20 (2-100) for facial non-inflammatory lesions, 69 (10-100) for facial cyst lesions, and 20 (11-97) for total lesion count, compared to Tretinoin's respective reductions of 90 (2-100), 8 (0-100), 55 (3-100), and 9 (2-82). The tertiary endpoint analysis using the ISGA Score at week 4 revealed that Combination Cream resulted in 3.5% of patients achieving Grade 0 (Clear) and 52.2% achieving Grade 1 (Almost Clear), whereas Tretinoin showed 0% for both grades. Additionally, 39.9% of Combination Cream users reached Grade 2 (Mild), compared to 19.4% for Tretinoin. The CADI Score at week 4 reflected that 5.0% of patients using Combination Cream were clear, 82.9% had mild symptoms, 22.0% had moderate symptoms, and none had severe symptoms. In contrast, Tretinoin users had 0% clear, 16.2% mild, 53.4% moderate, and 30.4% severe symptoms. The physician's global evaluation of efficacy showed that 23.8% of patients using Combination Cream were rated as excellent and 74.8% as good, with only 1.4% showing no change and none rated as poor or worse. For Tretinoin, 0.4% were rated as excellent, 25.3% as good, 31.2% showed no change, and 43.1% were rated as poor or worse.

Table 2. Primary and secondary efficacy of 2 types of therapy (Based on Retrospective Cohort)

Variable	Combination Cream* N = 774	Tretinoin 0.05% N = 253	p-value
Primary Endpoint			
Mean present change from baseline to week 4:			< 0,05
• Facial inflammatory lesion	26 (0 – 59)	23 (0 – 59)	
• Facial non-inflammatory lesion	9 (0 – 57)	4 (0 – 58)	
• Facial cyst lesions	2 (0 – 6)	1 (0 – 6)	
• Total lesion count	17 (5 – 84)	10 (0 – 60)	
Overall mean reduction in acne count at week 4			< 0,05
• Facial inflammatory lesion	90 (13 – 100)	90 (2 – 100)	
• Facial non-inflammatory lesion	20 (2 – 100)	8 (0 – 100)	
	69 (10 – 100)	55 (3 – 100)	

• Facial cyst lesions • Total lesion count	20 (11 – 97)	9 (2 – 82)	
Secondary Endpoint			
Mean present change from baseline to week 4 (by AI Measurement): • Spot • Pore • Wrinkle • UV Moist • UV damage • Roughness • Porphyrin • Pigmentation • Hydration	 5 (1 – 28) 5 (1 – 41) 3 (0 – 39) 9 (1 – 38) 7 (1 – 36) 6 (0 – 38) 5 (1 – 45) 5 (1 – 58) 10 (3 – 47)	 3 (0 - 24) 3 (0 – 39) 1 (0 – 28) 6 (0 – 37) 4 (0 – 26) 3 (0 – 26) 19 (1 – 46) 4 (0 – 26) 4 (1 – 37)	< 0,05
Overall mean reduction in acne count at week 4 (by AI Measurement): • Spot • Pore • Wrinkle • UV Moist • UV damage • Roughness • Porphyrin • Pigmentation • Hydration	 10 (3 – 68,3) 20,3 (12,2 – 75,9) 12,5 (7,8 – 60) 19,0 (7,2 – 54,3) 17 (9,1 – 70,0) 20 (3,4 – 64,4) 31,6 (7,5 – 70) 10 (2,2 – 65) 21,3 (2,9 – 63,3)	 6 (0 – 54) 10,34 (3,1 – 7,5) 3,5 (1,7 – 52,8) 10 (3,4 – 52,9) 11,3 (3,2 – 65) 10,5 (7,3 – 56,7) 9,9 (3,5 – 70) 8,1 (2,2 – 61,5) 9,1 (2,1 – 61,7)	
Tertiary endpoint			
ISGA Score at week 4, n (%) • Grade 0 (Clear) • Grade 1 (Almost Clear) • Grade 2 (Mild) • Grade 3 (Moderate) • Grade 4 (Severe)	 27 (3,5%) 404 (52,2%) 309 (39,9%) 34 (4,4%) 0	 0 0 49 (19,4%) 159 (62,8%) 45 (17,8%)	< 0,05
CADI Score at week 4, n (%) • Clear (0) • Mild (1-4) • Moderate (5-9) • Severe (10-15)	 39 (5,0%) 642 (82,9%) 170 (22,0%) 0	 0 41 (16,2%) 135 (53,4%) 77 (30,4%)	< 0,05
Physician's global evaluation of efficacy, n (%) • Excellent • Good • No Change • Poor • Worse	 184 (23,8) 579 (74,8%) 11 (1,4%) 0 0	 1 (0,4%) 64 (25,3%) 79 (31,2%) 109 (43,1%) 0	< 0,05

*Combination Cream: Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%.
ISGA: Investigators Static Global Assessment
CADI: Cardiff Acne Disability Index

An analysis of the side effects of the 2 types of therapy is presented in Table 3. There's no significant difference in all local side effects/ adverse events between single and combination cream (p value >0,05) while no systemic side effects are found in the study. Regarding adverse events by severity, the Combination Cream had 13 cases of mild adverse events (1.7%), while Tretinoin had 15 cases (5.9%). No moderate or severe adverse events were reported for either treatment. For local adverse events, both treatments showed similar profiles for burning, itching, and stinging. Combination Cream reported 5 cases of burning (0.6%), 2 cases of itching (0.3%), and 6 cases of stinging (0.8%). In comparison, Tretinoin reported 5 cases of burning (2.0%), 2 cases of itching (0.8%), and 6 cases of stinging (2.4%).

Table 3. Recapitulation of side effects or adverse events

Variable	Combination Cream* N = 774	Tretinoin 0.05% N = 253	p-value
Adverse Events by severity, n (%)			
• Mild	13 (1,7%)	15 (5,9%)	N/A
• Moderate	0	0	
• Severe	0	0	
Local Adverse Events, n (%)			> 0,05
• Burning	5 (0,6%)	5 (2,0%)	
• Itchy	2 (0,3%)	2 (0,8%)	
• Stinging	6 (0,8%)	6 (2,4%)	
• Eruptive Papules	-	-	
• Hypopigmentation	-	-	
• Hyperpigmentation	-	2 (0,8%)	
• Erythema	-	-	
• Scaling	-	-	
• Urticaria and Angioedema	-	-	
• Atrophy	-	-	
• Striae	-	-	
Systemic side effects are indirect or direct			N/A
• Constipation	-	-	
• Gastroesophageal reflux disorder	-	-	
• Urinary Tract Infection	-	-	
• Blood Glucose increased	-	-	
• Pyrexia	-	-	
• Upper respiratory tract infection	-	-	
• Blood Bilirubin increased	-	-	
• Swelling face	-	-	
• Blood cortisol increased	-	-	

*Combination Cream: Clindamycin 3%, Tretinoin 0.05%, and Dexamethasone 0.05%.
N/A: Not Applicable

DISCUSSION

Acne vulgaris is a disease of the pilosebaceous, which is a chronic inflammatory illness. The pilosebaceous unit is an immunocompetent organ that can respond to infection threats. In acne vulgaris, hyper-cornification; sloughed keratinocytes; and other debris block the follicular opening, make comedo, excess production of sebum, abnormal proliferation of *Propionibacterium acnes* (*P. acnes*), and infiltrate leukocytes in response to the inflammation (Berson & Shalita, 1995; Cunliffe, 1998; H. P. M. Gollnick et al., 1991; Toyoda & Morohashi, 2001b; Zouboulis & Piquero-Martin, 2003).

The inflammation phase starts when the sebaceous follicle becomes sensitive to any alteration. Microcomedone "lesions" in which an abnormal number of keratinized cells are formed are believed to be the earliest indicator of subclinical acne, although this is not fully understood. Keratinocytes and sebocytes secrete chemokines and proinflammatory cytokines, stimulating and recruiting lymphocytes and T-helper cells into infected sites, commencing intracellular communication/ signaling mechanisms, and determining subsequent protective immunological measures. In the case of inflammatory acne, both innate (nonspecific) and acquired (antibody-mediated) immune responses will be triggered (Jappe, 2003).

The subsequent proliferation of *P. acnes* within the blocked follicle causes this organism to discharge extracellular foreign material. Lipase is a proinflammatory that produces cytotoxic free fatty acid, protease, and hyaluronidase from sebum that can break the follicular wall, leaking to the dermis and induce inflammation. P. acnes can create porphyrins, a highly immunogenic protein that can generate hazardous oxygen species, free radicals, and highly comedogenic squalene peroxide after combining with oxygen (Burkhart et al., 1999; Farrar et al., 2000; Graham et al., 2004; Hoeffler, 1977; Holland et al., 1998; INGHAM et al., 1980; Puhvel & Reisner, 1972; Thomsen, 1980b; Van Vlem et al., 1996).

P. acnes releases decisive low molecular *weight* chemotactic factors and chemotactic lipases into the dermis and follicles during the first stages of pre-inflammatory and inflammatory acne. This process can draw diverse white blood cells, including neutrophils, lymphocytes, and monocytes, to the site of an infection. During early infection, *P. acnes* also increases the synthesis of proinflammatory small polypeptide cytokines, including granulocyte-macrophage colony-stimulating factor (GMCSF), interferon-gamma (IFN), tumor necrosis factor-alpha (TNF), and interleukin (IL) IL-1α, IL-1ß, IL-6, IL-8, and IL-12. These messenger molecules are produced in and around the damaged follicle as part of the defense of the skin and prevent infection from spreading (Brown & Shalita, 1998; Firmansyah et al., 2020, 2021; Webster et al., 1982).

In addition to the inflammatory challenge described above, additional innate and acquired immune responses are produced within the host, exacerbating the follicle's inflammation. Immunoreactive T lymphocytes (T-cells), CD4+ cells, and CD14+ cells infiltrate the inflammatory lesion. Active monocytes become macrophages and begin to encircle and ingest pathogen-associated foreign substances.

Intracellular neutrophil/ macrophage phagocytosis produces

enzymes and toxic compounds, such as reactive oxygen species, which help to prevent the destruction and elimination of *P. acnes* and its damaging extracellular products. When persistently and excessively produced, these substances can harm the follicle, enter the surrounding dermis, and inflame the host (Akamatsu et al., 1990, 1992; Camisa et al., 1982; Jappe et al., 2002; Jeremy et al., 2003; Liu et al., 2005; Miyachi et al., 1986; NORRIS & CUNLIFFE, 1988; Webster et al., 1980; WEBSTER et al., 1981; Webster & Kligman, 1979).

Leukotriene B4 (LTB4) and C5-derived neutrophil chemotactic factors are involved in pathogenic acne since they induce neutrophils, monocytes, and eosinophils to make inflammation. Some proinflammatory that also might aggravate the inflammation are Toll-like receptor (TLR), transcription factor activator protein 1 (AP-1), vascular cell adhesion, macrophage degranulation, growth factors, transglutaminase and lipoxygenase expression, cytokine modulation metalloproteinase activity in the dermis, prostaglandin synthesis, and possibly IL-5 (Choi et al., 2008; Czernielewski et al., 2001a; Fumarulo et al., 1991; Gille et al., 1997; Massey et al., 1978; Millikan, 2003; Shroot & Michel, 1997; Webster et al., 1978).

Topical retinoids (adapalene 0.1% and 0.3%; tazarotene 0.1%; tretinoin 0.01%, 0.025%, 0.038%, 0.04%, 0.05%, 0.08%, and 0,1% in the United States; isotretinoin 0.05% and 0.1% in other regions of the world) are used in acne therapy. Topical retinoids have been shown to reduce visible lesions and inhibit the growth of microcomedone. Retinoids correct desquamation by inhibiting keratinocyte growth and encouraging differentiation (Czernielewski et al., 2001b; Thielitz et al., 2001a, 2008). Significant inflammatory mechanisms such as toll-like receptors, leukocyte migration, and the AP-1 pathway are activated. Its molecular activity has been proven to be dose-dependent for adapalenes. Based on evidence, isotretinoin, tretinoin, and tazarotene also decrease the expression of Toll-like receptors. Blocking this route decreases inflammation by reducing the inflammatory cytokines and nitric oxide (Tenaud et al., 2007; Thielitz & Gollnick, 2008; Yeh et al., 2016).

The efficacy of topical retinoids increases as the concentration gets higher. Tretinoin is an example shown to have a dose-dependent effect in an animal model (Griffiths, Finkel, Tkanfaglia, et al., 1993). In two ultrastructural trials, 0.1% and 0.025% tretinoin reduced microcomedones by 80% and 35%, after 12 weeks of treatment (Thielitz et al., 2001b). Registration studies of 0.3% adapalene gel demonstrate greater dose-related effectiveness than adapalene gel, 0.1% across all effectiveness metrics, with tolerability at both dosages being satisfactory. Examination of the phase III trial of 0.3% adapalene gel revealed that patients with more lesions at the beginning of the trial saw the best efficacy (Pariser et al., 2005; Thiboutot et al., 2006).

Due to their action method in the dermis, topical retinoids have been proven to affect scarring, pigmentation, and central acne lesions. Acne scarring is caused by dermal remodeling and an imbalance between matrix degradation and matrix synthesis, both regulated by matrix metalloproteinases (MMPs) (Fabbrocini et al., 2010). Participants in an open-label pilot study using 0.3% adapalene for scarring demonstrated an improvement of one or two levels on a scar assessment and an overall improvement in skin texture by week 24. In addition, 0.3% adapalene was

related to activation of the procollagen gene and enhanced procollagen-1 and collagen-3 staining (J. Leyden et al., 2017).

In pigmentation disorders, retinoids diminish epidermal pigmentation by increasing epidermal turnover and lightening hyperpigmented lesions by preventing melanosome to keratinocytes (Pandya & Guevara, 2000). Grimes et al. observed that tazarotene 0.1% cream is helpful for acne-related post-inflammatory hyperpigmentation, lowering the intensity and area of pigmentation considerably over 18 weeks than the placebo (p-value = 0.05) (Grimes & Callender, 2006). In a study of 0.1% tazarotene cream compared to 0.3% adapalene gel, Tanghetti et al. showed that 16 weeks of tazarotene significantly lowered post-inflammatory hyperpigmentation in acne patients. Moreover, in 25% (10/40) of the participants treated with tazarotene, post-inflammatory hyperpigmentation ultimately resolved. In contrast, adapalene did not achieve a significant difference from baseline (Tanghetti et al., 2010). Griffiths et al. discovered that 0.1% tretinoin cream significantly reduced pigmentation in melasma patients compared to the placebo (P = 0.0006) (Griffiths, Finkel, Ditre, et al., 1993). In an open-label study with dark skin and acne from South Africa, 0.1% adapalene gel reduced the frequency of pigmented macules and density of hyperpigmentation to levels "similar to those reported with topical tretinoin" (Jacyk & Mpofu, 2001). Research from Bulengo-Ransby et al. In 40 weeks, hyperpigmentation lesions in patients treated with tretinoin were substantially lighter than in patients treated with a placebo (p-value < 0.001) (Bulengo-Ransby et al., 1993).

The prevailing consensus is that retinoids should be prescribed for acne. Previous randomized controlled trials proved that monotherapy with topical retinoids dramatically reduces inflammatory lesions, with effects comparable to noninflammatory lesions. The therapeutic effects on topical lesions of topical retinoids were demonstrated by patients' photos taken before and after having topical retinoid monotherapy. Leyden et al. evaluated the effect of topical retinoids on inflammatory lesions by analyzing high-resolution digital images of 577 patients enrolled in an enrollment study and treated with topical retinoids. Five blinded researchers evaluated the severity of acne before and after 12–15 weeks of topical retinoid monotherapy (tazarotene, adapalene, or tretinoin). All retinoids demonstrated a clinical improvement in inflammatory acne; additionally, the rate of improvement increased as acne severity increased. Jacobs et al. revealed in a recent comprehensive study that BPO and adapalene both exhibit a rapid beginning of effect (measured as a 25% time decrease in the mean number of inflammatory lesions) in contrast to other retinoids (tretinoin, topical isotretinoin) (Jacobs et al., 2014; J. Leyden et al., 2017; J. J. Leyden et al., 2005; A. Shalita et al., 1996; Webster et al., 2001, 2002).

Topical antimicrobials include clindamycin, erythromycin, tetracycline, dapsone, benzoyl peroxide, and azelaic acid. Those compounds have local adverse effects (AE) like erythema, desquamation, dryness, and burning. Benzoyl peroxide also bleaches hair, clothing, and bed linens (Haider, 2004).

Randomized controlled trials show evidence that is essential to justify the usage of topical acne

vulgaris. When inflammatory lesions (papules/pustules) are present, the Global Alliance recommends adding topical antimicrobials to topical retinoids as a first-line treatment for all kinds of acne. Topical retinoids are the preferred treatment for mild comedo acne (whiteheads/ blackheads). The most effective treatment for moderate comedonal acne and mild to moderate inflammation is a combination of topical benzoyl peroxide or retinoids and a topical antibacterial. The correct evaluation of a treatment's efficacy involves trials spanning 6 to 8 weeks or 8 to 12 weeks. Topical retinoids and topical antimicrobials are preferred to benzoyl peroxide and topical antimicrobials. In case of moderate to severe acne, using systemic medication is suggested (oral tetracyclines, isotretinoin, hormonal contraceptives, etc.) (H. Gollnick et al., 2003; D. R. Guay, 2007; Haider, 2004).

Topical antibacterial monotherapy is not suggested due to the slow onset of action and the potential for the formation of bacterial resistance, According to the medicine label, topical application of dapsone is not advised, except for glucose-6-phosphate dehydrogenase (G6PD) levels, which have been determined. Foam, gel, solution, and lotion formulations of 1% clindamycin are available in the United States, with two combination products: clindamycin phosphate 1.2% with tretinoin 0.025% gel and benzoyl peroxide 5% with clindamycin 1% gel/lotion. A gel formulation containing 0.025% tretinoin and 1% clindamycin is under investigation. Treatments with benzoyl peroxide/clindamycin combinations or clindamycin/tretinoin combinations in solution/ gel/ lotion form should normally be administered twice daily. This review focuses solely on the use of clindamycin in the treatment of acne vulgaris (D. Guay, 2007; D. R. Guay, 2007). In all 18 trials, topical clindamycin was statistically better than placebo for reducing the number of lesions and in investigator/patient assessment (Alirezaï et al., n.d.; Becker et al., 1981; Ellis et al., 1988, 2001; Fagundes et al., 2003; Gratton et al., 1982; Guin, 1981; Kuhlman & Callen, 1986; J. J. Leyden et al., 2001, 2006; Lookingbill et al., 1997; Rizer et al., 2001; A. R. Shalita et al., n.d.; Siegle et al., 1986; Thomsen, 1980a; Tschen et al., 2001).

The vehicle and salt form (hydrochloride versus phosphate) did not affect the effectiveness (Becker et al., 1981; Gratton et al., 1982; Guin, 1981). The findings were identical in both studies when clindamycin was given once or twice a day (Rizer et al., 2001). The formulation also had no significance in efficacy (Cunliffe et al., 2005) (in comparison of gel versus solution (Alirezaï et al., n.d.; Ellis et al., 1988), gel versus foam (A. R. Shalita et al., n.d.), and lotions versus solutions (Goltz et al., 1985)). Topical clindamycin seems to be as effective as or more effective than oral tetracycline or minocycline (Gratton et al., 1982), topical tetracycline (Resh & Stoughton, 1976), topical benzoyl peroxide (Swinyer et al., 1988) and topical erythromycin with/without zinc (Goltz et al., 1985; Schachner et al., 1990).

Combination therapies were statistically superior to their constituent monotherapies on all efficacy metrics (e.g., topical clindamycin was lesser than topical benzoyl peroxide/clindamycin (Ellis et al., 2001; Fagundes et al., 2003; J. J. Leyden et al., 2001, 2006; Tschen et al., 2001), tretinoin/clindamycin (J. J. Leyden et al., 2006), and

adapalene/clindamycin (Wolf et al., 2003; Zhang et al., 2004)). Topical monotherapy demonstrated less effectiveness compared to topical combination therapy: topical benzoyl peroxide versus topical benzoyl peroxide/ clindamycin (Fagundes et al., 2003; J. J. Leyden et al., 2001, 2006), topical tretinoin versus topical tretinoin/clindamycin (J. J. Leyden et al., 2006), topical clindamycin versus topical benzoyl peroxide/erythromycin.(Packman et al., 1996) On the other hand, the effectiveness of benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin is comparable (den Ley et al., 2001). Only in three studies were monotherapy and combination therapy similarly efficacious (clindamycin against benzoyl peroxide/clindamycin (Tucker et al., 1984) or tretinoin/clindamycin (Rietschel & Duncan, 1983), and tazarotene versus clindamycin/tazarotene (Tanghetti et al., 2006)).

In 1976, an efficacy comparison of the basic and phosphate salt versions of hydroalcoholic and N-methyl-2-pyrrolidone (NMP) medicines and vehicles was examined in a study involving 60 patients. At week 2/8, phosphate salts in NMP carrier, phosphate salts in hydroalcoholic carrier, base in NMP carrier, and base in hydroalcoholic carrier reduced the number of inflammatory papules by 44/80%, 32/55%, 41/75%, and 22/50%, respectively. At week 8, the proportions corresponding to no *P. acnes* growth in open comedones were 79, 46, 40, and 42%. In an experiment involving 45 patients, topical clindamycin phosphate 1% in NMP and hydroalcoholic vehicle was compared to 'standard' regimens, such as oral tetracycline. At week 2/8, inflammatory papules count decreased by 44/80%, 32/55%, and 18/27% respectively. Regrettably, in the same city, beneficiaries of topical clindamycin and conventional oral antimicrobials are treated at separate clinics (Stoughton & Resh, 1976).

A study in 1985 included 45 non-inflammatory acne cases (mainly women aged 14–15 years) that were treated with four different therapies (A = vitamin A 0.025% daily [n = 9]; B = benzoyl peroxide 5%/2% sulfur daily [n = 8]; C = clindamycin 1% once daily [n = 8]; and D = vitamin A acid 0.025% 3 days/week alternating with clindamycin 1% 4 days/week [n = 20]). The proportions of increase (where the increase was defined as a reduction in the number of comedones exceeding 50% after 3 months) were 64, 60, 48 and 65% (Rajka, 1985).

Three comparative clinical trials in 1998 using previously unreported data-on-file were published and demonstrated that once-daily of clindamycin gel 1.2%/tretinoin 0.025% was superior to twice-daily of clindamycin gel 1% and clindamycin lotion 1%. There were no significant differences in the percentage of reduction in inflammatory lesions between all the treatments. In two of the three investigations, the combination product was considerably more effective than clindamycin gel (64 vs. 51%; p = 0.04) and clindamycin lotion (69 vs. 61%; p = 0.05) at reducing the number of non-inflammatory lesions. In two of the three investigations, the combination product outperformed clindamycin gel (2.5 against 1.6; p = 0.001) and clindamycin lotion (2.9 versus 2.1; p = 0.007) in the amount of Cook-grade enhancement. Scaling and erythema were more prevalent in combination product receivers than clindamycin monotherapy because tretinoin, a keratolytic, was present in combination products (Cambazard, 1998).

Topical corticosteroids play a pivotal role in the treatment of numerous dermatological disorders. They are FDA-approved and suggested for inflammatory and pruritic skin disorders treatment. Indications using topical corticosteroids are psoriasis, vitiligo, eczema, atopic dermatitis, phimosis, acute dermatitis, lichen planus, lichen simplex chronicus, discoid lupus erythematosus, and lichen sclerosis (Ference & Last, 2009). They are also beneficial for hyperproliferative, immunological, and inflammatory disorders (Giannotti, 1988; Tan & Firmansyah, 2021b).

The mode of action of topical corticosteroids is for anti-inflammatory, antimitotic, and immunosuppressive actions. Topical corticosteroids have anti-inflammatory effects by vasoconstriction; phospholipase A2 suppression; and direct inhibition of DNA and inflammatory factors (Abraham & Roga, 2014; Ahluwalia, 1998).. Vasoconstriction in the upper dermis decreases the inflammatory mediation in the affected region (Ahluwalia, 1998). Lipocortin formation inhibits phospholipase A2 and decreases prostaglandins and leukotrienes, giving an anti-inflammatory effect. Other than acting directly at the DNA level to boost anti-inflammatory gene expression, topical corticosteroids also indirectly block inflammatory factors, such as NFkb, to reduce pro-inflammatory gene expression (Ahluwalia, 1998).

The anti-mitotic in the topical corticosteroids plays a significant role in psoriasis; it has been postulated that decreased epidermal mitosis is caused by an increase in lipocortin, a protein regulated by endogenous glucocorticoids. The dermis possesses an anti-mitotic action that suppresses cell proliferation and collagen formation (Uva et al., 2012). As an immunosuppressive agent, topical corticosteroids decrease humoral components and inhibit the maturation; differentiation; and proliferation of all immune cells (Uva et al., 2012).

According to ophthalmology research, topical steroids can treat conjunctiva, cornea, and anterior segment inflammation. Steroids may also be beneficial in treating uveitic or postoperative macular edema in specific conditions. Diffusion over the cornea allows penetration into the aqueous fluid (Doane et al., 1978). Dexamethasone is intrinsically about 25 to 30 times stronger than hydrocortisone (Meyer, 2013). Efficacy in any preparation is determined not just by the drug's intrinsic potency, but also by its penetration and staying power. Lipophilic agents (such as acetate) are more likely to penetrate the cornea deeper compared to less lipophilic agents (like phosphate preparation) (Shields & Shields, 2006). Even though prednisolone acetate is six times more potent on a molar basis compared to dexamethasone or betamethasone, 1% prednisolone acetate has a stronger anti-inflammatory impact than 0.1% dexamethasone or betamethasone phosphate. Since preservatives impair the tight connections between the corneal epithelial cells, solutions with preservatives have more penetration than those without (Cunningham & Wender, 2010). The frequency of application also increases the anti-inflammatory effect. A study of ocular inflammation found that applying topical prednisolone acetate every 15 minutes (or five doses at 1-minute hourly intervals) had a stronger anti-inflammatory impact than applying it hourly. It is critical to shake the suspension properly before using it,

otherwise, the dose will vary (Leibowitz & Kupferman, 1979).

Ophthalmology research even indicates long-term use of dexamethasone with continuous-release formulations. A biodegradable intravitreal implant containing 0.7 mg dexamethasone, OZURDEX, in the solid rod-shaped polymer drug delivery system NOVADUR. It is intended to release a greater dose in the first 6 weeks with a lower dose following over 3 to 6 months. Steroids are injected in a stepwise manner using a single-use intravitreal applicator. It is used for diabetic macular edema (DMO) treatment, central or branch retinal vein occlusion (CRVO, BRVO) that causes macular edema, and non-infectious posterior uveitis (Beer et al., 2003; Nguyen et al., 2012; Shaikh et al., 2013).

Acne is multifactorial, including hyperkeratosis and blackheads, sebum production, inflammation, and higher Propionibacterium acnes quantity and activity. Hyperkeratosis and comedones choke hair follicles, particularly those with big sebaceous glands (on the face, neck, chest, and back). This increases the amount of comedogenic and inflammatory components that produce acne lesions. The free fatty acid component development in the sebum induces irritation of the follicles and sebum thickening. Propionibacterium acnes is a follicular flora that participates in the inflammatory chemotactic process and the synthesis of lipolytic enzymes that alter the lipid portion of sebum (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

Acne manifests as open or closed comedones (non-inflammatory lesions) and as papules, pustules, or nodules (inflammatory lesions). Severe acne can result in systemic symptoms (known as acne fulminans) as well as non-systemic symptoms (known as acne conglobata). In most cases, severe acne resolves with scar tissue. Acne can impact negatively on the patient's mentality in varying degrees (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

Acne management should focus on the elements that contribute to its pathogenesis. According to the current agreement, acne treatment depends on the severity. Retinoids (topical tretinoin, adapalene, tazarotene, isotretinoin), antibiotics (tetracycline, minocycline, doxycycline, trimethoprim/sulfamethoxazole, clindamycin, erythromycin, daptomycin), selective aldosterone antagonists, estrogen/progestin combos, and other acne treatments are utilized. Diet is another nonpharmacological therapy to explore. It is recommended that patients avoid diets with low glycemic index and greasy meals. Common acne treatments include comedone extraction, intralesional steroid injections, and glycolic acid or salicylic acid peels. Blue light therapy might kill Propionibacterium acne by eliminating porphyrins in bacterial cells. Scar tissue caused by acne should be treated with skin surgery (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

Topical retinoids are comedolytic, inhibiting the production of microcomedones, the early stages seen in acne vulgaris. The target of retinoid activity is aberrant keratinocyte proliferation and differentiation, and it has an anti-inflammatory effect. Retinoids, which are vitamin A derivatives, help to avoid the production of comedones by normalizing follicular epithelial desquamation. Tretinoin, tazarotene, and adapalene are the

most common topical retinoids. Tretinoin is the most commonly utilized comedolytic and anti-inflammatory agent (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

Topical antibiotics are commonly used as an effective acne therapy. Clindamycin is a semi-synthetic chemical derived from the antibiotic Lincomycin. Clindamycin works by decreasing the amount of free fatty acids, reducing inflammation, and decreasing the number of propionibacteria. Clindamycin's anti-inflammatory characteristics specifically suppress Proprioninbacterum acne development, protein synthesis, lipase production, follicular production of free fatty acids, and leukocyte chemotaxis molecules (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

Corticosteroids enter cytoplasmic keratinocytes and other epidermal and dermal cells via the stratum corneum barrier and cell membranes. Corticosteroids are anti-inflammatory, immunomodulatory, anti-proliferative, and vasoconstrictive. Corticosteroids work as anti-inflammatory agents by inhibiting the activity of phospholipase A2, an enzyme responsible for prostaglandins, leukotrienes, and other arachidonic acid derivatives formation. Administering steroids aims to avoid inflammation that leads to scar formation/scar tissue production (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

As is well known, treating scar tissue caused by acne is still tough and expensive. In general, invasive therapy takes a long healing time since it involves the difficult synthesis of epidermal tissue again and the formation of collagen tissue in the skin. If the scars formed are ice pick and box, all processes such as laser therapy, subsection scar, and needling are ineffective. The point is that all scar therapies are still difficult, expensive, take a long time to heal, interfere with the activities of patients who are usually of productive age, and the results are still unsatisfactory. As a result, preventing the formation of scars is preferable to treating scars after they have formed (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

The steroid utilized topically in this combination is of the Dexamethasone type. We have heard that Dexamethasone is a steroid with low absorption; hence, dexamethasone is rarely employed in topical steroid therapy for various types of skin conditions that require topical steroids (Reginata et al., 2019). Because Dexamethasone's absorption is poor in the skin's layers, it might be why no one has ever used Dexamethasone in acne therapy until now. However, we use it in acne therapy because we discovered that because absorption into the epidermis layer is poor, it has the advantage that Dexamethasone "only" works on the surface of the skin and will only enter into the open pores (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

There has been a paradigm change from the pathophysiological idea of acne causes to therapy management, necessitating the formulation of this cream from the three active ingredients listed above. Biofilms, bacteria, toxins, and dysbiosis events from the microbiome are some of the components (interactions between numerous variables) that, according to the most recent theory, contribute to the development of acne because they result in the release of several metabolites that, individually and collectively, will induce irritation or serve as the basis

for acne. Due to the multifactorial nature of acne's etiopathogenesis, it would be prudent to employ a combination therapy than a single treatment (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

Night cream formulas are intended to keep the skin moist, encourage skin regeneration, and function so that it appears bright. Night cream also stimulates collagen formation, which improves skin suppleness. Night creams are typically made up of components that cannot be exposed to sunlight, resulting in thicker formulations (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

This cream is used as an anti-inflammatory, antibacterial, and comedolytic, which are the key components in the pathogenesis of acne, and it is manufactured in the form of a night cream to have an additional effect on skin regeneration. Apart from eradicating acne, this invention will make the facial skin brighter and its function will be preserved, which is especially crucial in preventing scars, which are tough to cure and the results have not been satisfying so far (Elizabeth et al., 2021; Reginata et al., 2019; Tan & Firmansyah, 2021a).

CONCLUSION

Acne is a problem that almost all humans experience. Therefore acne treatment requires innovation from time to time to provide better treatment with maximum results. This study tested 2 types of anti-acne drugs: Combination Cream (Clindamycin 3%, Dexamethasone 0.05%, and Tretinoin 0.05%) and Monotherapy Tretinoin 0.05% topically. Both drugs have good efficacy in treating acne with minimum side effects. The comparison between both drugs shows that Combination Cream (Clindamycin 3%, Dexamethasone 0.05%, and Tretinoin 0.05%) provides superior efficacy in terms of primary and secondary efficacy parameters in acne treatment.

Further research (especially randomized controlled study) regarding the use of combination cream for acne treament in Indonesian population is encouraged.

Ethical Clearance

Tarumanagara University Human Research Ethics Council Institute of Research and Community Engagement granted ethical approval for this study (Registration Number: PPZ20192057 and Letter Number: 1681-Int-DIR-KLPPM/Untar/X/2019). This study has been registered with ClinicalTrials.gov.

Inform Consent

The study was carried out following the Helsinki Declaration. Each patient and/or their parent or legal guardian signed informed consent/assent forms freely. The protocols were authorized by the Food and Drug Supervision Agency of the Republic of Indonesia and the Local Ethics Committee.

Availability of data and material

The datasets used and/or analyzed during the current investigation are available upon reasonable request from the corresponding author.

Conflict of Interest

The authors declared that they have no conflicts of interest.

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Consent For Publication

The author declared and consented that (a) the article has not been previously published elsewhere, neither the portions nor as a whole article, nor under consideration and will not be submitted for publication in another journal, and (b) all authors have consented to the publication of the article.

REFERENCES

Abraham, A., & Roga, G. (2014). Topical Steroid-Damaged Skin. *Indian Journal Of Dermatology*, *59*(5), 456. Https://Doi.Org/10.4103/0019-5154.139872

Afriyanti, R. N. (2015). Akne Vulgaris Pada Remaja. *Medical Faculty Of Lampung University*.

Ahluwalia, A. (1998). Topical Glucocorticoids And The Skin-Mechanisms Of Action: An Update. *Mediators Of Inflammation*, *7*(3), 183–193. Https://Doi.Org/10.1080/09629359891126

Akamatsu, H., Komura, J., Miyachi, Y., Asada, Y., & Niwa, Y. (1990). Suppressive Effects Of Linoleic Acid On Neutrophil Oxygen Metabolism And Phagocytosis. *Journal Of Investigative Dermatology*, *95*(3), 271–274. Https://Doi.Org/10.1111/1523-1747.Ep12484890

Akamatsu, H., Kurokawa, I., Nishijima, S., & Asada, Y. (1992). Inhibition Of Neutrophil Chemotactic Factor Production In Comedonal Bacteria By Subminimal Inhibitory Concentrations Of Erythromycin. *Dermatology*, *185*(1), 41–43. Https://Doi.Org/10.1159/000247401

Den Ley, J. J., Hickman, J. G., Jarratt, M. T., Stewart, D. M., & Levy, S. F. (2001). The Efficacy And Safely Of A Combination Benzoyl Peroxide/Clindamycin Topical Gel Compared With Benzoyl Peroxide Alone And A Benzoyl Peroxide/Erythromycin Combination Product. *Journal Of Cutaneous Medicine And Surgery*, *5*(1), 37–42. Https://Doi.Org/10.1177/120347540100500109

Farrar, M. D., Ingham, E., & Holland, K. T. (2000). Heat Shock Proteins And Inflammatory Acne Vulgaris: Molecular Cloning, Overexpression And Purification Of A Propionibacterium Acnes Groel And Dnak Homologue. *Fems Microbiology Letters*, *191*(2), 183–186. Https://Doi.Org/10.1111/J.1574-6968.2000.Tb09337.X

Graham, G. M., Farrar, M. D., Cruse-Sawyer, J. E., Holland, K. T., & Ingham, E. (2004). Proinflammatory Cytokine Production By Human Keratinocytes Stimulated With Propionibacterium Acnes And P. Acnes Groel. *British Journal Of Dermatology*, *150*(3), 421–428. Https://Doi.Org/10.1046/J.1365-2133.2004.05762.X

Gratton, D., Raymond, G., Guertin-Larochelle, S., Maddin, S., Leneck, C., Warner, J., Collins, J., Gaudreau, P., & Bendl, B. (1982). Topical Clindamycin Versus Systemic Tetracycline In The Treatment Of Acne. *Journal Of The American Academy Of Dermatology*, *7*(1), 50–53. Https://Doi.Org/10.1016/S0190-9622(82)80009-1

Griffiths, C. E. M., Finkel, L. J., Ditre, C. M., Hamilton, T. A.,

Ellis, C. N., & Voorhees, J. J. (1993). Topical Tretinoin (Retinoic Acid) Improves Melasma. A Vehicle-Controlled, Clinical Trial. *British Journal Of Dermatology*, *129*(4), 415–421. Https://Doi.Org/10.1111/J.1365-2133.1993.Tb03169.X

Griffiths, C. E. M., Finkel, L. J., Tkanfaglia, M. G., Hamilton, T. A., & Voorhees, J. J. (1993). An In Vivo Experimental Model For Effects Of Topical Retinoic Acid In Human Skin. *British Journal Of Dermatology*, *129*(4), 389–394. Https://Doi.Org/10.1111/J.1365-2133.1993.Tb03163.X

Grimes, P., & Callender, V. (2006). Tazarotene Cream For Postinflammatory Hyperpigmentation And Acne Vulgaris In Darker Skin: A Double-Blind, Randomized, Vehicle-Controlled Study. *Cutis*, *77*(1), 45–50.

Kraft, J., & Freiman, A. (2011). Management Of Acne. In *Cmaj. Canadian Medical Association Journal* (Vol. 183, Issue 7). Canadian Medical Association. Https://Doi.Org/10.1503/Cmaj.090374

Kuhlman, D. S., & Callen, J. P. (1986). A Comparison Of Clindamycin Phosphate 1 Percent Topical Lotion And Placebo In The Treatment Of Acne Vulgaris. *Cutis*, *38*(3), 203–206.

Leibowitz, H. M., & Kupferman, A. (1979). Optimal Frequency Of Topical Prednisolone Administration. *Archives Of Ophthalmology*, *97*(11), 2154–2156. Https://Doi.Org/10.1001/Archopht.1979.01020020472014

Leyden, J. J., Berger, R. S., Dunlap, F. E., Ellis, C. N., Connolly, M. A., & Levy, S. F. (2001). Comparison Of The Efficacy And Safety Of A Combination Topical Gel Formulation Of Benzoyl Peroxide And Clindamycin With Benzoyl Peroxide, Clindamycin And Vehicle Gel In The Treatments Of Acne Vulgaris. *American Journal Of Clinical Dermatology*, *2*(1), 33–39. Https://Doi.Org/10.2165/00128071-200102010-00006

Leyden, J. J., Krochmal, L., & Yaroshinsky, A. (2006). Two Randomized, Double-Blind, Controlled Trials Of 2219 Subjects To Compare The Combination Clindamycin/Tretinoin Hydrogel With Each Agent Alone And Vehicle For The Treatment Of Acne Vulgaris. *Journal Of The American Academy Of Dermatology*, *54*(1), 73–81. Https://Doi.Org/10.1016/J.Jaad.2005.04.046

Leyden, J. J., Shalita, A., Thiboutot, D., Washenik, K., & Webster, G. (2005). Topical Retinoids In Inflammatory Acne: A Retrospective, Investigator-Blinded, Vehicle-Controlled, Photographic Assessment. *Clinical Therapeutics*, *27*(2), 216–224. Https://Doi.Org/10.1016/J.Clinthera.2005.02.009

Puhvel, S. M., & Reisner, R. M. (1972). The Production Of Hyaluronidase (Hyaluronate Lyase) By Corynebacterium Acnes. *Journal Of Investigative Dermatology*, *58*(2), 66–70. Https://Doi.Org/10.1111/1523-1747.Ep12551495

Purwaningdyah, R. A. K. (2013). Profil Penderita Akne Vulgaris Pada Siswa-Siswi Di Sma

Shafiyyatul Amaliyyah Medan. *E-Jurnal Fakultas Kedokteran Usu*, *1*(1).

Rajka, G. (1985). On Therapeutic Approaches To Some Special Types Of Acne. *Acta Dermato-Venereologica. Supplementum*, *120*, 39–42.

Schachner, L., Pestana, A., & Kittles, C. (1990). A Clinical Trial Comparing The Safety And Efficacy Of A Topical Erythromycin-Zinc Formulation With A Topical Clindamycin Formulation. *Journal Of The American Academy Of Dermatology*, *22*(3), 489–495. Https://Doi.Org/10.1016/0190-9622(90)70069-T

Shaikh, A. H., Petersen, M. R., Sisk, R. A., Foster, R. E., Riemann, C. D., & Miller, D. M. (2013). Comparative Effectiveness Of The Dexamethasone Intravitreal Implant In Vitrectomized And Non-Vitrectomized Eyes With Macular Edema Secondary To Central Retinal Vein Occlusion. *Ophthalmic Surgery, Lasers And Imaging Retina*, *44*(1), 28–33. Https://Doi.Org/10.3928/23258160-20121221-09

Shroot, B., & Michel, S. (1997). Pharmacology And Chemistry Of Adapalene. *Journal Of The American Academy Of Dermatology*, *36*(6), S96–S103. Https://Doi.Org/10.1016/S0190-9622(97)70050-1

Siegle, R. J., Fekety, R., Sarbone, P. D., Finch, R. N., Deery, H. G., & Voorhees, J. J. (1986). Effects Of Topical Clindamycin On Intestinal Microflora In Patients With Acne. *Journal Of The American Academy Of Dermatology*, *15*(2), 180–185. Https://Doi.Org/10.1016/S0190-9622(86)70153-9

Tschen, E. H., Katz, H. I., Jones, T. M., Monroe, E. W., Kraus, S. J., Connolly, M. A., & Levy, S. F. (2001). A Combination Benzoyl Peroxide And Clindamycin Topical Gel Compared With Benzoyl Peroxide, Clindamycin Phosphate, And Vehicle In The Treatment Of Acne Vulgaris. *Cutis*, *67*(2), 165–169.

Tucker, S. B., Tausend, R., Cochran, R., & Flannigan, S. A. (1984). Comparison Of Topical Clindamycin Phosphate, Benzoyl Peroxide, And A Combination Of The Two For The Treatment Of Acne Vulgaris. *British Journal Of Dermatology*, *110*(4), 487–492. Https://Doi.Org/10.1111/J.1365-2133.1984.Tb04664.X

Uva, L., Miguel, D., Pinheiro, C., Antunes, J., Cruz, D., Ferreira, J., & Filipe, P. (2012). Mechanisms Of Action Of Topical Corticosteroids In Psoriasis. *International Journal Of Endocrinology*, *2012*, 1–16. Https://Doi.Org/10.1155/2012/561018

Van Vlem, B., Vanholder, R., De Paepe, P., Ringoir, S., & Vogelaers, D. (1996). Immunomodulating Effects Of Antibiotics: Literature Review. *Infection*, *24*(4), 275–291. Https://Doi.Org/10.1007/Bf01743360

Webster, G. F., Berson, D., Stein, L. F., Fivenson, D. P., Tanghetti, E. A., & Ling, M. (2001). Efficacy And Tolerability Of Once-Daily Tazarotene 0.1% Gel Versus Once-Daily Tretinoin 0.025% Gel In The Treatment Of Facial Acne Vulgaris: A Randomized Trial. *Cutis*, *67*(6 Suppl), 4–9.